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Synthesis and Pesticidal Evaluation of Novel Quin-8-Oxytetramethyldiphenyldioxaphosphonine Analogue

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ABSTRACT

Although a great deal of success has been achieved in the synthesis of dibenzodioxaphosphepin derivatives during the last few decades with the introduction of hundreds of its six-, and seven-membered ring systems, the search for more practical agronomic pesticides that is readily available and of good activity, remains attractive and important to an agronomic chemist. During the course of the development of synthetic routes to a promising pesticide, a facile preparation for a nine-membered heterocyclic dibenzodioxaphosphonine compound was discovered. Previously reported compounds consist of six- and seven-membered ring systems. The pure product was fully characterized by spectroscopic [IR, NMR (^{1}H, ^{13}C, ^{31}P) and Mass] analyses. The pure compound possesses a LC_{50} value of 19.3 μg cm^{-3} in a brine shrimp lethality assay (BST). The preliminary field study on the cowpea weevil bioassay shows 51% success. Details of the synthetic route as well as bioassay results are reported herein.

KEYWORDS

Dibenzodioxaphosphonine, candidate, BST, LC_{50}.

The world population requires food supply for growth and development. Efforts of farmers in this regard must not be underemphasized. However, pests constantly jeopardize their efforts and diseases also destroy farm produce.[1] One of the most common pests is the striped bean weevil, which causes a great loss of legumes each year. It feeds on the flowers, stem foliage, flower buds and green buds, causing a complete crop loss within a short time, thereby causing decrease in the yield of beans. The pest infests the crops in the field and in storage where it bores holes into the seeds and turns them to an unusable powdery mass, thereby rendering the product unmarketable.[2]

Over the years, scientists have sought ways of combating the menace of bean pests and diseases. Cowpea is a key staple food for many developing countries to supplement their protein demand. The pesticidal properties of the organophosphorous compounds have stimulated a great deal of interest in investigating them as agrochemicals.[3] Slight variations in the structure of organophosphorous compounds affect their efficiency due to the fact that the interaction of the enzyme with a substrate is very sensitive to the size, shape and polarity of the molecule.[4]

Five-, six- and seven-membered heterocycles containing phosphor, nitrogen, oxygen and sulphur have been successfully synthesized and proved to be cholinesterase inhibitors as well as possessing an appreciable degree of antitumor properties.[5–8] Organophosphorous heterocyclic compounds are inexpensive to make, easy to apply and lethal to a wide variety of pests. They appear to be the miracle pesticides with broad-spectrum characteristics.[9] Attempts were made in our laboratory to develop a narrow-spectrum agronomic pesticide that will selectively work against the targeted organism while causing minimum damage to the host (plants).

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Experimental

General Procedure

Solvents were dried over sodium wire and distilled. Chromatographic purification using a silica gel column (Merck, 70–230 mesh, 60 A, BET surface area 500 m^2 g^{-1}, pore volume 0.75 cm^3) was used. Thin layer chromatography (TLC) was carried out on plates coated with silica gel (Merck, TLC grade), and viewed under ultraviolet lamps (254 and 365 nm). Spots were also detected with iodine vapour.

Melting points were determined on a GallenKemp apparatus (UK), and are uncorrected. Brine shrimp eggs were obtained from Artermia Inc., USA, and instant sea salt was purchased from the aquarium systems Serrebourg, France. IR spectra were recorded on a Perkin Elmer Pe 781 spectrophotometer in nujol mulls and using KBr discs. ^{1}H NMR data were recorded on a Varian EM-390 and FX 100 MHz (Joel LTD) using TMS as internal standard. ^{13}C NMR spectra were recorded on GE model GN-500 operating at 125 MHz. ^{31}P NMR spectra were recorded on a Brucker WM-300 instrument operating at 121.4 MHz, using $CDCl_3$ and DMSO-d_6 as solvents. FAB- mass spectra were taken using a Finnigan 4610 instrument at 70 eV in a DCl-Isobutane matrix.

Synthesis

Synthesis and isolation were carried out according to the method of Naidu *et al.*[8] with slight modification of the reaction conditions and reagents. A solution of 15.35 g (100 mmol) of phosphorylchloride in 100 cm^3 of dry benzene was made up in a 250 cm^3 three-neck round bottom flask equipped with a separating funnel and reflux condenser fitted with a $CaCl_2$ guard tube. The flask was heated on an oil bath and stirred by means of a hot plate/magnetic stirrer. A solution of 14.50 g (100 mmol) of

8-hydroxyquinoline and 10.15 g (100 mmol) of anhydrous triethylamine in 100 cm^3 of dry benzene was added dropwise through a separating funnel. The addition took 60 min and the whole solution was refluxed with vigorous stirring for 10 h. The solid triethylammonium chloride was filtered off and the solvent from the filtrate was recovered under reduced pressure. A dark brown viscous filtrate was obtained and subjected to fractional distillation under reduced pressure. The major fraction distilled at 125–128°C/5 mm Hg (literature boiling point is 95°C/0.1 mm Hg) and was collected as a colourless glassy viscous liquid (**2**) weighing 12.98 g (46%).

Equivalent mols (5 mmol) of quin-8-oxyphosphorodichloridate (**2**) in 25 cm^3 of dry benzene was added dropwise over a period of 45 min. to a stirred solution of 1.85 g (5 mmol) of $\alpha,\alpha,\alpha',\alpha'$-tetramethyl-2,2′-biphenyldimethanol (**1**) and 1.01 g (10 mmol) of anhydrous triethylamine in 50 cm^3 of dry benzene at room temperature. After the addition, the temperature of the reaction mixture was raised to reflux temperature by heating with continued stirring for 5 h. The progress of the reaction was monitored by TLC analysis of the starting material and the reaction mixture.

The reaction mixture was cooled and solid $Et_3N.HCl$ was filtered off and the solvent removed using a rotary evaporator. The crude compound was then subjected to column chromatography using a mixed solvent system [chloroform/methanol (1:1)] to obtain a semi-pure compound. The semi-pure compound obtained was isolated by washing repeatedly with water, n-hexane, petroleum ether (40–60°C) and propan-2-ol, respectively. Recrystallization of this compound from propan-2-ol gave pure white granules of 1.73 g (75.7%) **3**; m.p. 190–191°C. (Scheme 1).

Compound **3**: δ_H (500 MHz, DMSO-d_6) 2.15 (12H, s,15,16,17,18-Me), 7.25–8.10 (14H, m, ArH), δ_P (121.4 MHz, DMSO-d_6) 44.0, δ_C (125 MHz, DMSO-d_6) 18.7 (C-16, C-17), 18.9 (C-17, C-18), 81.0 (C-13, C-14), 130–123 (C-1–C-12), 160–125 (C-2′–C-10′), m/z (%): 459 (0) (M+), 447(3), 325.2(3), 236(25), 157.3(100), 79.1(62), $C_{27}H_{26}NO_4P$ (459.148) (Calculated: C 70.59, H 5.70, N 3.05. Found C 70.48, H 5.63, N 3.03).

Brine Shrimp Lethality Bioassay (BST)

This was performed according to Meyer *et al.*[11]. Instant ocean sea salt (2.28 g) was dissolved in 60 cm^3 of distilled water. Fifty milligrams of shrimp eggs obtained from *Artermia salina* Inc., California, was added in a hatching chamber. The hatching chamber was placed under a fluorescent light for 48 h. Twenty milligrams of test sample was weighed and dissolved in 2 cm^3 of DMSO. From the solution, 500, 50 and 5 μL were transferred into labelled vials corresponding to 1000, 100 and 10 $\mu g\ cm^{-3}$, respectively. The experiment was conducted in triplicate at each dosage with one control containing 500 μL of the solvent. The vials were left overnight to evaporate at room temperature. Exactly 4 cm^3 of instant ocean sea salt was added to each vial followed by 10 larvae of brine shrimp (48–72 h after initiation of hatching). Immediately after the addition of shrimps, the final volume in each vial was adjusted to 5 cm^3 using sea salt solution.

The vials were left for 24 h after which the surviving shrimps at each dosage were counted and recorded. BST LC_{50} were determined at 95% confidence interval by analysing the data on Pentium 686 Y2K-compliant computer loaded with a 'Finney program'.[10–11]

Cowpea Weevils (*Callosobruchus maculatus)* Bioassay

The bioassay procedure adopted was described by Fatope *et al.*[13] with some modifications. *Callosobruchus maculatus* individuals were obtained from IITA office in Kano, Nigeria. Cowpea weevils were reared on jars. Approximately 20 g of cowpea was apportioned to each Pyrex Petri dish. The test sample (dibenzodioxaphosphonine **3**) was mixed with deionized water in the appropriate proportion. Three conical flasks of cowpea were assigned to receive a particular concentration of aqueous test sample; 20, 40, 60 and 80%. Untreated controls and controls treated with deionized water were used; 750 μL of the treatment were added to the 20 g of cowpea in a Pyrex Petri dish. The dish was covered and shaken vigorously for 10 s to thoroughly coat the cowpeas. The cowpeas were allowed to dry for 10 s on a Whatmann No. 1 filter paper. The cowpeas were then transferred to an appropriately labelled 250 mL conical flask, and 10 adult *C. maculatus* individuals (0–24 h after adult emergence) were placed in each flask. Each flask was covered with cotton wool. All three flasks in a treatment, received a test sample solution from the same stock of the appropriate concentration. Observations were made and recorded after 20, 40 and 60 days. Correction for death in the control experiment was made using Abbott's equation:

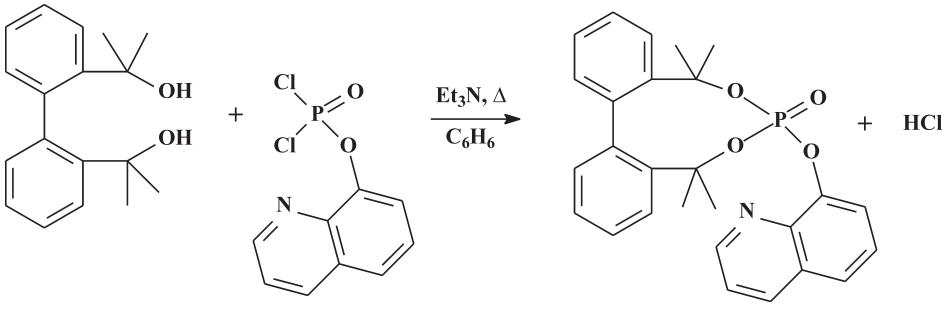
$$\%\ \text{Control} = \frac{\%\ \text{Dead (treated group)} - \%\ \text{Dead (untreated group)}}{100 - \%\ \text{Dead (untreated group)}}$$

Results and Discussion

The synthetic route paved the way for the preparation of a nine-membered ring dibenzodioxaphosphonine (**3**) which showed enhanced pesticidal properties when compared to the literature values reported[7,6] for six- and seven-membered ring systems.

The synthesis of quin-8-oxytetramethyldiphenyldioxaphosphonine (**3**) was accomplished by the reaction of equimolar cyclocondensation of $\alpha,\alpha,\alpha',\alpha'$-tetramethyl-2,2′-biphenyldimethanol (**1**) with quin-8-oxylphosphorodichloridate (**2**) in the presence of anhydrous triethylamine as scavenger of HCl and benzene as solvent (Scheme 1).

The novel compound (**3**) has the molecular formula



1 **2** **3**

Scheme 1

$C_{27}H_{26}NO_4P$. The IR spectrum showed the presence of P=O stretching vibrations in the region of 1280 cm^{-1}. The P-O-C aryl group gives rise to two bands due to the stretching frequency of the C–O bond of the aryl group and stretching frequency of the P–O bond. The compound under investigation shows these absorptions in the region 1245–1200 cm^{-1}. The medium and sharp band in the region 970–940 cm^{-1} which are characteristics of P-O-C aromatic group present in this molecule.[12] The ^{1}H NMR spectrum recorded in DMSO-d_6 shows signals for four methyl groups (δ 2.15, 4 × CH_3) as well as the expected signals for aromatic protons around 7.2–8.10 ppm. ^{31}P NMR spectrum was also determined in DMSO-d_6 and showed a peak at 44.0. ^{13}C NMR spectrum showed the expected carbon signals. The MS spectrum gave m/z = 459 (M+).

The LC_{50} value observed for the compound was 19.3 μg cm^{-3}. This value indicates improved pesticidal properties, when compared with that of six-membered ring organophosphorous heterocyclic compounds. The preliminary field study of the synthesized compound on the cowpea weevil shows an appreciable activity (51% success) using a standard method[13] for stored farm produce.

There is no doubt that quin-8-oxytetramethyldiphenyldioxaphosphonine synthesized is useful as pesticide based on this study. This compound appears to be of better toxicity than the five-, six- and seven-membered ring heterocycles previously reported. We hope this work will encourage more organometalic chemists to consider the nine-membered ring system as useful building blocks for more potent and selective agronomic pesticides.

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